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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040318

Application Number: 09/915,694
Filing Date: July 25, 2001
Appellant(s): BANDMAN ET AL.

Richard C. Ekstrom
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 09, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 3, 6, 7, 9, and 12 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Attwood et al. Comput. Chem. 2001, Vol. 25(4), pp. 329-39.

Ponting. Brief. Bioinform. March 2001, Vol. 2(1), pp. 19-29.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 – Written Description

Claims 3, 6, 7, 9, and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompass any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2 (claim 12).

The specification, however, only provides the following representative species encompassed by the invention: an isolated polynucleotide consisting of SEQ ID NO: 2. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these polynucleotides by any identifying structural characteristics or properties for which no predictability of structure is apparent.

Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full,

clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Claims 6, 7, and 9 which depend from claim 3 are also rejected because they do not correct the defect of claim 3.

Claim Rejections - 35 USC § 112 - Enablement

Claims 3, 6, 7, 9, and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention encompass any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2 (claim 12).

The specification provides guidance and examples for making an isolated polynucleotide consisting of SEQ ID NO: 2. However, the specification does not teach the specific structural/catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered. The state of the art as exemplified by Attwood et al. (Comput. Chem. 2001, Vol. 25(4), pp. 329-39) is such that "...we do not fully understand the rules of protein folding, so we cannot predict protein structure; and we cannot invariably diagnose protein function, given knowledge only of its sequence or

structure in isolation" (reference is attached to the Office Action dated 12/17/2002). Furthermore, Ponting (Brief. Bioinform. March 2001, Vol. 2(1), pp. 19-29) states that "...predicting function by homology is a qualitative, rather than quantitative, process and requires particular care to be taken...due attention should be paid to all available clues to function, including orthologue identification, conservation of particular residue types, and the co-occurrence of domains in proteins" (reference is attached to the Office Action dated 12/17/2002).

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed polynucleotide is enormous and undue and entails selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in any polynucleotide to make a polynucleotide encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 or selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in the nucleotide sequence of SEQ ID NO: 2 to make a polynucleotide that has a nucleotide sequence that is at least 95% identical to SEQ ID NO: 2 and determining by assays whether the encoded polypeptide has malate dehydrogenase activity.

The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for enzyme structure and activity/function which must be preserved. Thus, searching for the specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in a

polynucleotide to make the claimed polynucleotide is well outside the realm of routine experimentation and predictability in the art of success in determining whether the resulting polypeptide has activity is extremely low since no information is provided by the specification regarding the specific catalytic amino acids and the structural motifs essential for enzyme structure and activity/function which must be preserved.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific catalytic amino acids and the structural motifs essential for activity/function which must be preserved. Without such a guidance, the experimentation left to those skilled in the art is undue. Claims 6, 7, and 9 which depend from claim 3 are also rejected because they do not correct the defect of claim 3.

(11) Response to Argument

A. Written Description

Appellants argue beginning on page 5 of the Brief that one of ordinary skill in the art would recognize polynucleotides that have nucleotide sequences that are at least 95% identical to SEQ ID NO: 2 or polynucleotides that encode polypeptides having an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 since the nucleotide sequence of SEQ ID NO: 2 and the amino acid sequence of SEQ ID NO: 1 are disclosed in the specification. Appellant thus conclude that the specification provides an adequate written description of the claimed invention.

Appellants argue in pages 5-7 that a common basis for which courts have found claims to DNA to be invalid is the recitation of functional properties of a DNA without the definition of structural features of the DNA. Appellants summarize cases *Fiers v. Revel*, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993) and *University of California v. Eli Lilly* and Co., 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). Appellant argue that in contrast to Lily and Fiers cases where nucleic acids that were defined on the basis of functional characteristics alone did not meet the written description requirement of 35 U.S.C. § 112, 1st Paragraph, the claims at issue define the nucleic acid by structure alone rather than on functional characteristics. Appellants conclude that the Office Action fails to explain how the claims of the instant invention are different from the nucleic acid claims of the Lily and Fiers cases which were found to be invalid.

Appellant argue in page 8 that the present claims do not define a "highly variant" genus. Appellants cite the Brenner et al. reference to demonstrate that the claimed genus is of narrow scope. Appellants state that the Brenner et al. reference teaches an analysis of proteins with known structural and functional relationship indicates that 30% identity over at least 150 amino acid residues between two amino acid sequences is reliable in establishing evolutionary homology and that 40% identity over at least 70 residues is a reliable in "signifying homology between proteins". Appellants thus argue that only mitochondrial malate dehydrogenases having 30% identity over at least 150 residues of SEQ ID NO: 1 instead of all potential mitochondrial malate dehydrogenases "related to SEQ ID NO: 1" would be encompassed by the claimed genus.

Appellants argue on pages 8-9 that the state of the art has advanced since the time of filing of the cited cases of *Lilly* and *Fiers* and the present application. Appellants cite the invention of polymerase chain reaction (PCR), efficient cloning and sequencing of DNA, and compilation of large protein and nucleotide sequence databases. Appellants conclude that one of skill in the art would recognize given the amino acid sequence of SEQ ID NO: 1 and the amino acid sequence of SEQ ID NO: 2 that the inventors were in possession of the claimed invention.

Appellants conclude that defining the claimed genus by structural terms, i.e. nucleotide sequence, is all that is required to meet the written description requirement 35 U.S.C. § 112, first paragraph.

Appellants' arguments have been fully considered but are not found to be persuasive for several reasons. A review of the language of claims 3 and 12 indicates that the claimed invention is drawn to a genus of polynucleotides with widely differing structural, chemical, and physical characteristics. The genus is highly variable because a significant number of structural differences between genus members is permitted as evident by the recitation that the claimed polynucleotides have a nucleotide sequence that is 95% identical to the nucleotide sequence of SEQ ID NO: 2 and the recitation that the claimed polynucleotides encode polypeptides that have an amino acid sequence which is at least 95% identical to SEQ ID NO: 1. The claimed genus encompasses a wide breadth of polynucleotides with widely differing biological functions such as

encoding proteins and enzymes. Furthermore, the claimed genus encompasses polynucleotides with biological functions that have yet to be discovered.

Appellants' argument that the explicit disclosure of the amino acid sequence of SEQ ID NO:1 and the nucleotide sequence of SEQ ID NO: 2 is sufficient to meet the written description requirement is not persuasive since the genus is highly variable and encompasses a wide breadth of polynucleotides with widely differing structural, chemical, physical, and biological properties. The instant application discloses only one species encompassed by the claimed genus which is an isolated polynucleotide consisting of SEQ ID NO: 2 which is disclosed as encoding a malate dehydrogenase having the amino acid sequence of SEQ ID NO: 1. The specification fails to describe additional representative species of the claimed genus. The specification does not provide a written description all the polynucleotides as encompassed by the claimed genus and their biological functions which have yet to be discovered. In absence of any recitation of function in the claims, one of skill in the art cannot determine which polynucleotides are or are not described by the specification.

The claims of the instant application differ from the claims of the Lilly and Fiers cases in that the claims of the instant application recite a specific nucleotide sequence (SEQ ID NO: 2) and a specific amino acid sequence (SEQ ID NO: 1) while the claims of the *Lilly* and *Fiers* cases as reported by the Appellants recite no specific nucleotide of amino acid sequence but rather a nucleic acid encoding a specific protein. A description of the claimed genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides falling within the scope of the genus.

Alternatively, description of the claimed genus of polynucleotides may be achieved by recitation of a correlation of structural features to functional properties that are common to the members of the genus. However, the instant claims do not recite any structure to function correlation and the specification only discloses one member of the claimed genus which is the nucleotide sequence of SEQ ID NO: 2.

Appellants' argument that in view of the Brenner et al. reference the claims do not define a highly variant genus but rather a genus of narrow scope is not persuasive since the claims do not recite the limitation that the claimed polynucleotide encode malate dehydrogenases that have 30% identity to SEQ ID NO: 1 or that the claimed polynucleotide has 30% identity to SEQ ID NO: 2 and encodes a malate dehydrogenase. Furthermore, it cannot be concluded that all potential malate dehydrogenases "related to SEQ ID NO: 1" as stated by Appellants are to be explicitly excluded from the claimed genus since the claims do not recite this exclusion. The Examiner's position regarding the Brenner et al. reference is that it provides an analysis of how to estimate and assign evolutionary homology and functional homology to polypeptides by comparing amino acid sequences, and that the Brenner et al. reference does not teach when polynucleotides are or are not members of the claimed genus of the instant invention.

While Appellants' statement that the state of the art has advanced since the time of filing of the cited cases of Lilly and Fiers and the present application is valid, it is not apparent that the invention of PCR, efficient cloning and sequencing of DNA, and compilation of large protein and nucleotide sequence databases would enable one of

skill in the art to determine which polynucleotides are or are not described by the specification.

Given the lack of additional representative species as encompassed by the claimed genus, the wide breadth of polynucleotides with widely differing structural, chemical, physical, and biological functions, and the lack of reciting any particular structure to function or activity relationship in the claims; one of skill in the art would not recognize from the disclosure that Appellants were in possession of the claimed genus of polynucleotides. Claims 6, 7, and 9 which depend from claim 3 are also rejected because they do not correct the defect of claim 3. Hence, claims 3, 6, 7, 9, and 12 do not meet the written description requirement of 35 U.S.C. § 112, first paragraph.

B. Enablement

Appellants argue beginning on page 10 of the Brief that the specification describes how to make and use naturally-occurring polypeptide variants of SEQ ID NO: 1 and polynucleotide encoding such variants where the claimed variants are any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2. Appellants argue that the claimed polynucleotides may be identified by PCR techniques and hybridization techniques that were well known to those skilled in the art at the time of filing of the instant application or described in the specification of

the instant application. Appellants argue that one skilled in the art need not make and test vast numbers of polypeptides and that screening of cDNA libraries using appropriated PCR or hybridization conditions or by changing the composition or sequence of the probe or nucleic acid is all that is required to make the claimed invention.

Appellants argue on page 12 that the Attwood et al. reference and the Ponting reference is not relevant to making the claimed polynucleotides which in turn could be used in expression profiling and drug testing.

Appellants cite in page 12 the Brenner et al. reference which teaches an analysis of proteins with known structural and functional relationship indicates that 30% identity over at least 150 amino acid residues between two amino acid sequences is reliable in establishing evolutionary homology and that 40% identity over at least 70 residues is a reliable in "signifying homology between proteins". Appellants argue on page 13 that potential mitochondrial malate dehydrogenases (MT-MDH) may exist which have as little as 30% identity over at least 150 amino acid residues of SEQ ID NO: 1 but the claims recite "95% variants" which is less variation than that of all potential MT-MDH proteins related to SEQ ID NO: 1. Appellants conclude that one would expect that the claimed invention to have functional activities of a MT-MDH protein.

Appellants conclude that contrary to the standard as set forth in the cited case *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) where the first paragraph of § 112 ***requires nothing more than objective enablement*** (Appellants' emphasis added),

that the Examiner has failed to provide reasons to doubt the guidance of the specification.

Appellants' arguments have been fully considered but are not found to be persuasive for several reasons. A review of the language of claims 3 and 12 indicates that the claimed invention encompasses any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2.

Appellants' arguments that one skilled in the art need not make and test vast numbers of polypeptides and that screening of cDNA libraries using appropriated PCR or hybridization conditions or by changing the composition or sequence of the probe or nucleic acid is all that is required to make the claimed invention are not found to be persuasive since such guidance is not guidance for making the claimed invention but rather searching and screening for the claimed polynucleotides. In order to meet the enablement requirement, the specification must provide guidance as to the specific amino acid residues in the amino acid sequence of SEQ ID NO: 1 which cannot be changed and amino acid residues which can be changed but still retain malate dehydrogenase activity. However, the specification does not provide such guidance on how to make the claimed invention.

Thus, one skilled in the art would have to empirically determine the catalytic amino acids and the structural motifs essential for malate dehydrogenase activity which cannot be altered. This undue amount of experimentation is outside the realm of routine experimentation and entails selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in any polynucleotide to make a polynucleotide encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 or selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in the nucleotide sequence of SEQ ID NO: 2 to make a polynucleotide that has a nucleotide sequence that is at least 95% identical to SEQ ID NO: 2 and determining by assays whether the encoded polypeptide has malate dehydrogenase activity.

The recitation of "naturally occurring amino acid sequence" in the claims does not meet the enablement requirement since the specification must still provide guidance regarding the specific amino acid residues in the amino acid sequence of SEQ ID NO: 1 which cannot be changed and amino acid residues which can be changed but still retain malate dehydrogenase.

Appellants' arguments that the Attwood et al. reference and the Ponting reference is not relevant to making the claimed polynucleotides are not found to be persuasive because the cited references of Attwood et al. and Ponting provide rational and scientific explanations of the pitfalls in predicting or assigning any biological function base solely on a polynucleotide sequence or a deduced amino acid sequence.

Thus, one skilled in the art would be appraised of the difficulties in making the claimed invention.

Appellants' arguments that the Brenner et al. reference supports a conclusion that the claimed polynucleotide encoding a polypeptide having an amino acid sequence that is 95% identical to SEQ ID NO: 1 would have malate dehydrogenase activity are not found to be persuasive. The Brenner et al. reference does not teach one skilled in the art how to make the claimed invention. The Brenner et al. reference does not teach that any polypeptide having an amino acid sequence that is 95% identical to SEQ ID NO: 1 must have malate dehydrogenase activity. The specification does not explicitly state that homology to a reference polypeptide known in the prior art is a disclosure that the claimed polypeptide has the properties and biological function of the reference polypeptide relied upon.

The Brenner et al. reference simply provides an analysis of how to estimate and assign evolutionary homology and functional homology to polypeptides by comparing amino acid sequences. However, Attwood et al. teach "...we do not fully understand the rules of protein folding, so we cannot predict protein structure; and we cannot invariably diagnose protein function, given knowledge only of its sequence or structure in isolation".

Therefore, for the reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of written description and lack of enablement and it is believed that the rejections should be sustained.

Respectfully submitted,

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March 22, 2004

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